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LETTERS TO THE EDITOR

Ethical Committees and Noninformed Consent

Condorelli et al. (1) reported the results of a randomized, multicenter clinical trial that compared sulodexide with standard therapy in 3,986 survivors of acute myocardial infarction. First, we were very surprised that the control patients did not receive aspirin, which is obviously very effective in this setting. Moreover, aspirin treatment was an exclusion criteria. In the Discussion section of their report, the authors justify the absence of an aspirin-treated arm by the fact that when the trial was designed (in 1985), published reports had not yet shown a "clear benefit from antithrombotic therapy in terms of survival" (1). There is no indication of the actual trial duration, but we can infer from the text that the trial was not stopped prematurely because of increasing evidence of the beneficial effect of aspirin in post–myocardial infarction patients. Hence, because of the large number of patients randomized and the relatively few centers involved, the reader can infer that the randomization process was continued even after the results of the ISIS-2 trial (2) were published. If this is true, then several "control" patients did not receive effective treatment because they were used as control subjects for a potentially beneficial one. We wonder why the Ethical Committee or the Safety Monitoring Board did not stop the trial in view of the important new disclosures of the ISIS-2 investigators. Second, with regard to the "written informed consent" that the patients gave before randomization, we suspect that the consent form was not updated after the disclosure of the ISIS-2 results; otherwise, we do not understand why a patient would choose to enter a trial that deliberately denied (to half of the patients) a life-saving treatment.

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2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349–60.

Reply

In reply to Fresco et al., we would like to point out the following considerations. The IPO-V2 trial (1) began on March 8, 1985 and ended on December 30, 1989. The recruitment period was concluded, therefore, on January 1, 1989. The results of the ISIS-2 trial were published in August 1988 (2). Thus, the vast majority of patients in the IPO-V2 trial had already been enrolled by that time.

With regard to the remaining patients who entered our study after the results of the ISIS-2 trial were made public, the Ethical Committee decided that even though the ISIS-2 was an important and well-conducted study, pending further confirmation of its results by other investigators the decision to stop the trial or to add aspirin to both arms of the study was not warranted. In retrospect, and in view of the debate concerning the use of aspirin in the management of post–myocardial infarction patients, we consider the decision of the Ethical Committee quite appropriate. We hope that these considerations will be shared by the readers of the Journal.

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Nonlinearity of Left Ventricular End-Systolic Wall Stress–Velocity of Fiber Shortening Relation

Banerjee et al. (1) assert that the relation between end-systolic stress (ESS) and the mean rate-corrected velocity of shortening (VCF_c) is nonlinear for any constant contractile state and should not be used as an index of contractility. I do not believe that the data reported by Banerjee et al. support this finding. There are also other problems with this study.

Nonlinearity of the ESS–VCF_c relation. We investigated (2) this relation over a wide range of afterload, sampling 6 to 10 different levels of afterload at a constant contractile state in each subject. The regression was linear and the slope was similar in different subjects by linear and nonlinear regression analysis. Banerjee et al. cite only our original investigation (2), but these findings have been substantiated in numerous subsequent investigations (3–10) in humans and in animals. Banerjee et al. propose that this large body of accumulated data are incorrect on the basis of theoretic derivation of the ESS–VCF_c relation from the V_{max} index described by Sonnenblick and a flawed analysis of their own data.

Although Banerjee et al. state that the ESS–VCF_c relation is derived from V_{max}, this is incorrect. The ESS–VCF_c relation uses a mean normalized velocity, not a peak absolute velocity, and assesses afterload as end-systolic stress instead of the instantaneous stress at the instant of peak velocity. In an elegant series of experiments by Suga et al. (3), end-systolic stress has been shown to be the force limiting shortening and to hold no constant relation to stress at any point earlier in the cardiac cycle. The V_{max} is an isovolumic phase index, whereas ESS–VCF_c is an ejection phase index. Much of the V_{max} curve

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is obtained by extrapolation in contrast to the direct measurement of the ESS–VCF_c relation. There is no known mathematic or physiologic principle that would predict that the nonlinearity of V_{max} implies that ESS–VCF_c is nonlinear. The derivation of the afterload- and preload-adjusted shortening ($S_m-\sigma_{ed}-\sigma_{aft}$) and shortening rate ($SR_m-\sigma_{ed}-\sigma_{aft}$) from the systolic myocardial stiffness concept of Mirsky et al. (11,12) is far more relevant. In a series of investigations, we and others (5,9,10) found $S_m-\sigma_{ed}-\sigma_{aft}$ to be linear, and we observed parallel shifts in the slope of the regression with increased or decreased contractility. When analyzed from an appropriate theoretic point of reference, the ESS–VCF_c relation would indeed be expected to be linear.

In their study, Banerjee et al. (1) collected two data points at each contractile state, one at baseline and a single point at higher afterload. On the basis of these two data points, they speculate that the curve connecting them is nonlinear, particularly outside of the observed data range. There is no valid analysis that permits one to conclude that a regression of two points is linear or nonlinear nor to conclude anything concerning the shape of the curve outside the observed range. Investigations performed by us (2,5,9,10) and by others (3,4,6–8) have involved multiple observations collected over a much wider range of afterload values, allowing critical examination of the potential nonlinearity of this relation, and none was found.

Interanimal variability of the ESS–VCF_c relation. Banerjee et al. describe a "large and significant interanimal variability" of the slope of the ESS–VCF_c relation based on connecting two points, a method that does not allow an estimate of the goodness of fit or a statistical estimate of the confidence interval for the slope. When we and others (2–8) obtained the slope from multiple levels of afterload over a broad range of afterload, we found no statistically significant difference in the slope value between individuals.

Nonparallel shifts of the ESS–VCF_c regression slope. The observation that led Banerjee et al. to speculate that the ESS–VCF_c relation is nonlinear was the finding that during dobutamine infusion they observed an apparent increase in the slope of the ESS–VCF_c relation. The correct method of analysis would be to compare the slope of the ESS–VCF_c regression for any individual subject at baseline with that observed during dobutamine infusion. Banerjee et al. cannot perform this analysis because they have insufficient data points for statistical analysis and are left with zero degrees of freedom for either the regression or the comparison of slopes.

During low dose infusions of dobutamine, we observed (2 [Fig. 6]) a trend toward steeper (but still linear) regressions. In our more recent work (5,9,10) using midwall analysis, we found that the slope of the midwall velocity versus afterload regression does not change with altered contractility. This apparent difference between midwall and endocardial shortening velocity appears related to the finding that endocardial shortening overestimates average transmural fiber shortening (10). This effect is augmented at higher end-systolic wall thicknesses, as seen during hypertrophy and enhanced contractility.

The point that Banerjee et al. seem to miss is that we never used the *slope* of the ESS–VCF_c relation as an index of contractility; rather, we used the *position* of the relation with respect to the normal range. It should be noted that, similar to our findings, they did not find an overlap of data ranges between subjects with normal and enhanced contractility.

Investigation of the ESS–VCF_c relation at low afterload. Banerjee et al. (1) state that "At low afterloads, the curvilinearity of this relation becomes more apparent. Previous studies have not investigated the relation at low afterload, evaluating contractility only at normal and increased (during methoxamine infusion) afterload." Banerjee et al. used exactly the same approach that we did (afterload enhancement only for any given contractile state) and therefore did not investigate the relation at low afterload for any given contractile state. In agreement with our previous findings (2), they observed a decrease in afterload from baseline levels during dobutamine infusion. This does not permit conclusions concerning the behavior of the relation at reduced afterload for a constant contractile state. When the behavior of the relation at reduced afterload but constant contractile state was investigated by infusion of nitroprusside (4,8), the relation was observed to be linear, in contrast to the speculations of Banerjee et al.

Thus, it appears that Banerjee et al. have been misled by incorrect methods of analysis. Further definition of the limitations and shortcomings of the ESS–VCF_c relation as an index of contractility is needed, but the report by Banerjee et al. only undermines that process.

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Reply

Dr. Colan grossly misstates our findings when he states that we concluded "the relation between end-systolic stress (ESS) and the mean rate-corrected velocity of shortening (VCF_c) . . . should not be used as an index for contractility" (1). Conversely, we stated that "the